Draft Guidance for Industry, Clinical Laboratories, and FDA Staff

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In Vitro Diagnostic Multivariate Index Assays

DRAFT GUIDANCE

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For questions regarding this document contact Courtney Harper at 240-276-0490 ext.162 (courtney.harper@fda.hhs.gov).

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

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In Vitro Diagnostic Multivariate Index Assays

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Introduction

This guidance addresses the definition and regulatory status of a class of In Vitro Diagnostic Devices referred to as In Vitro Diagnostic Multivariate Index Assays (IVDMIAs).

The guidance also addresses premarket pathways and postmarket requirements with respect to IVDMIAs. As is true for all medical devices, regulatory classifications are driven by intended use(s) and device risk.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required

Background

The definition of a device is set forth at section 201(h) of the Food, Drug and Cosmetic Act ("the Act"). It provides in relevant part: "The term 'device' . . . means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals . . . ." (21 USC 321(h)). As described further in this guidance document, an IVDMIA is a test system that employs data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software, to generate a result that diagnoses a disease or condition or is used in the cure,

mitigation, treatment, or prevention of disease. An IVDMIA is therefore a device within the meaning of the Act.

FDA is aware of some confusion about the regulation of IVDMIAs that are developed by, and used in, a laboratory. We believe this confusion derives in part from FDA's approach to regulation of laboratory-developed tests that use commercially available ASRs and other commercially available, FDA-regulated components. FDA seeks to dispel the existing confusion and clarify its approach to regulation of IVDMIAs with this guidance document.

Some of the apparent confusion is associated with the Analyte Specific Reagent (ASR) rule,[1] which classifies and regulates ASRs that move in commerce. The rule does not extend to tests developed in-house by clinical laboratories using commercially available ASRs and used exclusively by that laboratory or ASRs created in-house and used exclusively by that laboratory for in-house testing. (62 FR 62243, 62249) While FDA stated in the preamble to the final ASR rule that "clinical laboratories that develop [in-house] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the Act," 62 FR 62249, FDA chose not to extend the rule to such tests and it has generally exercised enforcement discretion over laboratory-developed ASRs and laboratory-developed tests that use commercially available and laboratory-developed ASRs.

FDA took this approach because it believed it was regulating "the primary ingredients of most in-house developed tests," and because it believed that laboratories certified as high complexity under the Clinical Laboratory Improvement Amendments (CLIA), 42 USC 263a, "have demonstrated expertise and ability *to use ASRs* in test procedures and analyses." 62 FR 62249 (emphasis added).

FDA believed it was regulating the primary ingredients of most in-house tests because it was regulating the common elements of in-house tests, including most ASRs (21 CFR 864.4020), general purpose reagents (21 CFR 864.4010), general purpose laboratory equipment (21 CFR 862.2050), other laboratory instrumentation (21 CFR Part 864, subpart D), and controls (21 CFR 862.1660). IVDMIAs include elements, as described in the section on "Definition and Regulatory Status of IVDMIAs" of this guidance, that are not among these primary ingredients of in-house tests and that, therefore, raise safety and effectiveness concerns.

Also, as stated above, FDA decided to exclude laboratory-developed tests from the ASR rule due to its confidence in high-complexity laboratories' ability to use ASRs. The manufacture of an IVDMIA involves steps that are not synonymous with the use of ASRs and that are not within the ordinary "expertise and ability" of laboratories that FDA referred to when it

[1] "The ASR rule" refers to three rules. The rules, published in 1997, include rules that define and classify ASRs (21 CFR § 864.4020), impose restrictions on the sale, distribution, and use of ASRs (21 CFR § 809.30), and establish requirements for ASR labeling (21 CFR § 809.10(e)). The ASR rule was designed to accomplish several policy objectives. These include ensuring the quality of materials used as components of in-house tests, and providing appropriate labeling so that healthcare users would understand how these tests were being validated. 62 FR 62244. FDA adopted the approach of regulating most ASRs using general controls and exempting them from premarket notification requirements as the least burdensome approach.

promulgated the ASR rule. Therefore, IVDMIAs do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion. IVDMIAs must meet pre- and post-market device requirements under the Act and FDA regulations, including premarket review requirements in the case of class II and III devices.

The Least Burdensome Approach

This guidance document reflects our careful review of what we believe are the relevant issues related to IVDMIAs and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

Definition and Regulatory Status of IVDMIAs

For purposes of this guidance, IVDMIAs are test systems[2] that employ data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease. IVDMIAs reflect the following characteristics:

1. Use clinical data -- including data from one or more in vitro assays and, in some cases, demographic data -- to empirically identify variables and to derive weights or coefficients employed in an algorithm;
2. Employ the algorithm to integrate these variables in order to calculate a patient-specific result (e.g., a "classification," "score," or "index"). This result cannot be independently derived and confirmed by another laboratory without access to the proprietary information used in the development and derivation of the test; and
3. Report this result, which cannot be interpreted by the well-trained health care practitioner using prior knowledge of medicine without information from the test developer regarding its clinical performance and effectiveness.

Even if a laboratory or other IVDMIA manufacturer physically or procedurally separates the analyte measurement portion of the test system (i.e. the first step described above) from the calculation portion of the test system (i.e. the second step described above), the two parts are inextricably linked in obtaining the patient-specific result that is reported in the third step. A physician could not use the variables derived in step one for the intended use of the test absent the algorithm that integrates them to calculate the patient-specific result. Likewise, the physician could not use the algorithm without the assay portion of the test system (step one) as specified by the manufacturer. Use of the complete test system -- assay and algorithm -- is required to obtain a meaningful test result.

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[2] FDA considers a product a test system when it has some or all of the products needed to conduct a particular test, such as reagents, controls, equipment, software, etc., and/or it is one of these products and has instructions for use in a test. In the preamble to the ASR rule, FDA described a test system as having a proposed intended use, indications for use, instructions for use, and performance characteristics. 62 FR 62243, 62244. Use of the term "test system" in this guidance document is not linked with use of the term in 42 CFR Part 493.

Premarket and Postmarket Requirements for IVDMIAs

1. 510(k) or PMA?

Pursuant to section 513 of the Act, FDA will take a risk-based approach to the regulation of IVDMIAs. (21 USC 360c(a)(1)) Classification of an IVDMIA would depend on its intended use(s) and on the level of control necessary to assure the safety and effectiveness of the device. Class I medical devices are usually exempt from premarket review and rely on general controls to assure the safety and effective of low risk devices. Class II medical devices typically require premarket notification in the form of a 510(k) submission. Class III devices require the submission of an application for Premarket Approval (PMA). [see http://www.fda.gov/cdrh/devadvice/3132.html for additional information on device classifications].

We believe most IVDMIAs will be either class II or III devices. For example, a device intended as an indicator of a patient's risk of cancer recurrence may be a class II device, while the same device intended to predict which patients should receive chemotherapy might require Premarket Approval.

Safety and effectiveness determinations would include review of the performance of the entire test system, including directions for use and expected analytical or clinical performance, rather than a review of only certain subcomponents. As described above, use of the entire test system is required to obtain a meaningful test result. Regulation of the IVDMIA test system as a whole is consistent with the regulation and classification of other test systems, including clinical chemistry test systems (21 CFR Part 862, Subpart B) and clinical toxicology test systems (21 CFR Part 862, Subpart D). FDA has also previously regulated as entire systems laboratory-developed tests intended to detect drugs of abuse in hair samples and laboratory-developed tests intended to diagnose HIV.

We recommend that you contact the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) if you have questions regarding the classification of your IVDMI assay and for the type of information you need to submit for pre-market clearance or approval.

2. Investigational Use of IVDMIAs

Clinical investigations using human specimens conducted in support of premarket submissions for IVDMIA are subject to the human subject investigations requirements of 21 CFR 812.3(p). During this investigational phase, the safety and effectiveness of the product are being studied; i.e., the clinical performance characteristics and expected values are being determined in the intended patient population(s). These products must be labeled, "For Investigational Use Only. The performance characteristics of this product have not been established." 21 CFR 809.10(c)(2)(ii). Depending on the nature of the study initiated, sponsors may require an approved investigational device exemption (IDE) (21 CFR Part 812).

FDA recommends sponsors interact with the agency early and often in the development of these diagnostic assays and utilize appropriate scientific, medical, and statistical expertise to assure that thresholds of safety and effectiveness are addressed in submissions provided to FDA. OIVD recommends use of the pre-IDE process (protocol review) to help facilitate the regulatory process.

3. Post Market Requirements

IVDMIAs are subject to the Quality System Regulation (QSR) set forth at 21 CFR Part 820. FDA will work with laboratories that manufacture IVDMIAs and that must meet CLIA requirements to identify the least burdensome approach to compliance with the QSR. We recommend that laboratories identify instances where they believe compliance with a particular CLIA requirement may demonstrate compliance with a QSR requirement. FDA intends to issue guidance to assist laboratories that manufacture IVDMIAs in complying with the QSR.

IVDMIA manufacturers are also subject to the requirements of the Medical Device Reporting (MDR) regulation. (21 CFR Part 803) Laboratories are currently subject to certain provisions of the MDR regulation in their capacity as device user facilities. (21 CFR 803.3) User facilities are required to report to FDA and the device manufacturer information that reasonably suggests that a device has caused or contributed to the death of a patient. (21 CFR 830.30(a)(1)) User facilities must also report to the device manufacturer, or if not known, to the FDA, information that reasonably suggests a device may have contributed to a serious injury. (21 CFR 803.30(a)(2)) Manufacturers have some additional reporting requirements, including submission of reports of serious injury directly to FDA and submission of reports of device malfunction to FDA. (21 CFR 830.50(a)) The agency intends to issue further guidance to assist laboratories that manufacture IVDMIAs in complying with the MDR provisions that apply to manufacturers.